II. REMARKS

Formal Matters

Claims 32-36, 38, 39, and 45 are pending after entry of the above-noted amendments.

Claims 32-36, 38, and 39 were examined and were rejected. Claims 40 and 42-45 were withdrawn from consideration.

Claims 40 and 42-44 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, first paragraph

Claims 32-36, 38, and 39 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The instant specification provides ample description as to how to make and use a claimed composition.

The instant specification provides ample description as to how to make and use an IIS.

The instant specification states that IIS reduce the immunostimulatory effect of ISS. The Specification, page 7, lines 4-11 states:

> The IIS-ON of the invention reduce the immunostimulatory effect of ISS-ODN. Structurally, ISS-ODN are non-coding oligonucleotides 6 mer or greater in length which may include at least one unmethylated CG motif. The relative position of each CG sequence in ISS-ODN with immunostimulatory activity in certain mammalian species (e.g., rodents) is 5'-CG-3' (i.e., the C is in the 5' position with respect to the G in the 3' position). Many known ISS-ODN flank the CG motif with at least two purine nucleotides (e.g., GA or AA) and at least two pyrimidine nucleotides (e.g., TC or TT) to enhance the B lymphocyte stimulatory activity of the immunostimulatory polynucleotide (see, e.g., Krieg, et al, Nature, 374:546-549, 1995).

The instant specification also notes that ISS have been implicated in the onset and exacerbation of autoimmune disease. Specification, page 7, lines 22-24 states:

> Interestingly, a CpG containing oligonucleotide comparable to bacterial ISS-ODN has also recently been implicated in the onset and exacerbation of autoimmune disease through an IL-12 dependent pathway (Segal, et al, J. Immunol., 158:5087 (1997)).

The instant specification states that IIS reduce the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18, e.g., in the context of treating autoimmune disorders. Specification, page 21, lines 6-8; page 22, lines 1-3, 11-13, 22, and 23; and page 23, lines 11-16. Furthermore, the instant specification teaches how to determine whether an IIS will reduce the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18. Specification, page 8, line 17 to page 9, line 7.

The instant specification provides ample description of IIS. Specification, page 10, line 8 to page 13, line 11. The instant specification describes how to determine whether a given nucleic acid reduces the immunostimulatory effect of an ISS, and thus exhibits immunoinhibitory activity. Specification, page 8, line 17 to page 9, line 13; and Examples I-III.

The instant specification states that an IIS can be conjugated to an autoantigen or an autoantibody. Specification, page 18, lines 9-14; and page 18, line 14 to page 19, line 2. The specification describes various conjugation methods, a number of which were known in the art as of the priority date of the instant application. Specification, page 19, line 19 to page 20, line 2.

Finally, the instant specification provides ample description of how to administer an IIS or an IIS conjugate. Specification, page 21, line 1 to page 24, line 22. The instant specification provides a description of how to determine whether a Th2-type immune response has been induced. Specification, page 21, lines 11-16.

The Office Action stated that "Applicants point to areas of the specification that are not on point to the claimed invention" and stated that "Applicants argue that the ISS can be conjugated." Office Action, page 3.

However, as noted above, the specification describes how IIS can reduce the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18, e.g., in the context of treating autoimmune disorders, and that an IIS can be conjugated to an autoantigen or an autoantibody. The instant claims recite that IIS are conjugated to an autoantigen or an autoantibody, and that the nucleic acid inhibits production of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18. Thus, the cited portions of the specification would appear to be on point with respect to the claimed invention.

The instant specification provides working examples of the immunoinhibitory effect of a subject immunoinhibitory nucleic acid.

For example, Example I shows *in vitro* inhibition of ISS-stimulated proliferation of mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS. Example II shows *in vitro* inhibition of ISS-stimulated production of IFN-γ by mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS.

Example III shows *in vivo* induction of a Th2 immune response in mice. Mice were primed with the model antigen β-galactosidase (β-Gal) plus either an IIS or an ISS. Mice were subsequently challenged with β-Gal, and indicators of Th1 (e.g., IgG2a) and Th2 (e.g., IgE; IgG1) were measured. As shown in Figure 5, priming with IIS and β-Gal resulted in production of higher levels IgE when mice were challenged with β-Gal, compared to IgE levels produced by mice primed with ISS and β-Gal and challenged with β-Gal. In addition, as discussed in Example III, high levels of IgG2a antibodies (indicators of a Th1-type immune response) and low levels of IgG1 (indicators of a Th2-type immune response) were induced in response to β-Gal challenge in (ISS + β-Gal)-primed mice, while the low levels of IgG2a antibodies and high levels of IgG1 antibodies were induced in response to β-Gal challenge in (IIS + β-Gal)-primed mice.

Thus, the working examples provide both *in vitro* and *in vivo* evidence of the effect of IIS on inducing a Th2-type immune response.

The Office Action stated that "[t]he argued examples are not inhibition of autoimmune directed cells, the claimed invention is not demonstrated to be efficacious either in vitro or in vivo, or in any in vitro model that is predictive of in vivo efficacy." Office Action, page 3.

However, as previously explained:

1) the effects demonstrated in the working examples are include inducing a Th2-type immune response;
2) the art recognizes that generation of a Th2 type immune response is effective to treat autoimmune disease;
3) those skilled in the art would find it reasonable to expect that an IIS-autoantigen conjugate would induce a Th2-type immune response, and would be effective in treating an autoimmune disease.

Those skilled in the art would reasonably expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

As noted above, the instant specification provides ample evidence that an IIS induces a Th2-type immune response *in vivo*. Those skilled in the art would reasonably expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

The Office Action stated that "[t]his is not persuasive, the skill in the art at the time of the invention in 1997 clearly thought that immune deviation was unpredictable, could exacerbate autoimmune disease and that administration of autoantigen would exacerbate autoimmune disease." Office Action, page 3.

However, the instant claims *do not recite administration of an autoantigen*. Instead, the instant claims recite a pharmaceutical composition comprising an IIS conjugated to an autoantigen or an autoantibody. The instant composition induces a Th2-type immune response to an autoantigen, thereby ameliorating an autoimmune disorder.

The Office Action stated that Cho is not persuasive because "developments after the filing date [of] the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing." Office Action, page 4.

However, it is well established that post-filing references can provide evidence of enablement, e.g., where the post-filing references describe successful carrying out of a method described in a patent application, or successful use of a composition described in a patent application. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing; however, post-filing date publications can be used as evidence that the disclosure was in fact enabling when filed.[1]

The Office has not provided sufficient scientific rationale as to why one of ordinary skill in the art would not be able to make and use the invention as claimed.

1) The May 28, 2008 Office Action stated that the "the example [Example 3] does not establish inhibition of the immune response." May 28, 2008 Office Action, page 5.

However, as noted above, the instant specification provides working examples of the immunoinhibitory effect of a subject IIS. As discussed above, evidence was provided that an IIS induces a Th2-type immune response *in vivo*, as evidenced by production of IgE antibodies and IgG1 antibodies, which are hallmarks of a Th2-type immune response.

Furthermore, one aspect of an IIS conjugate as claimed is that it is capable of inducing a Th2-type immune response in an individual. Applicants showed that an IIS induces a Th2-type immune response *in vivo*.

There is no reason to believe that an IIS conjugate would not induce a Th2-type immune response. In fact, as noted above, there are ample scientific reasons why an IIS conjugate would induce a Th2-type immune response.

2) The May 28, 2008 Office Action stated that "the art does not recognize that generation of a Th2 type immune response is effective to treat autoimmune disease." May 28, 2008 Office Action, page 5.

However, the art does in fact recognize that generation of a Th2 type immune response is effective to treat autoimmune disease. The following references are illustrative.

a) **Young et al. (2000) *J. Immunol.* 164:3563; "Young"**

Young discusses the effect of Th2 cytokines in inhibition of experimental autoimmune encephalitis (EAE) in an animal model of multiple sclerosis (MS). Young states that EAE is induced in mice by adoptive transfer of activated proteolipid protein peptide (PLP) 139-151-specific Th1 cells. Young, page 3562, column 1, first paragraph. Young further states that T cells responding to altered peptide ligands (APL) of PLP, previously shown to induce Th2 differentiation and regulate disease in PLP-immunized mice, do not transfer EAE. Young presents data showing that Th2 cytokines can effectively down-regulate the encephalitogenic potential of PLP-spleen cells. Young concludes that induction of Th2 cytokines could be of potential therapeutic benefit in the treatment of disease mediated by autoimmune encephalitogenic T cells. Young, page 3571, column 2, third paragraph.

b) **Ho et al. (2003) *J. Immunol.* 171:4920; "Ho 2003"**

Ho 2003 (a copy of which was previously provided) discusses the use of an immunomodulatory GpG oligonucleotide in ameliorating autoimmune disease in an experimental autoimmune encephalitis (EAE) mouse model of multiple sclerosis (MS). Ho 2003states that EAE is a Th1-mediated animal disease model of MS. Ho 2003, page 4920, column 2, second full paragraph. Ho 2003states that the immunomodulatory GpG motif-containing oligonucleotide (IMO) stimulates the proliferation of Th2 cells. Ho 2003, page 4920, column 2, third full paragraph. Ho 2003 demonstrated that the IMO suppressed autoantigen-mediated EAE. Ho 2003, Figure 7; and page 4924, column 1, paragraph 1, to page 4925, column 2, paragraph 1.

Thus, Ho 2003provides further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

---

[1] *In re Brana* 34 USPQ2d 1436, 51 F.3d 1560, 1567 (Fed. Cir. 1995)

c) **Ho et al. (2005) *J. Immunol.* 175:6226; "Ho 2005"**

Ho 2005 (a copy of which was previously provided) discusses the use of a mixture of autoantigen and an immunomodulatory GpG oligonucleotide ("GpG ODN") to ameliorate autoimmune disease in an EAE mouse model of MS. Ho 2005 states that the immunomodulatory GpG-ODN counteracted the CpG-induced inflammatory effect in a Th1-mediated autoimmune disease by skewing both the autoaggressive T cell and B cell responses toward a protective Th2 phenotype. Ho 2005, Abstract.

Ho 2005 provides data showing that a combination of GpG ODN (IIS) and autoantigen shifted an immune response toward a Th2-type immune response, and resulted in amelioration of an autoimmune disorder. Those skilled in the art would reasonably expect that, as disclosed in the instant specification, an autoantigen-IIS conjugate would also shift an immune response toward a Th2-type immune response; and would therefore be useful in an autoimmune disease.

d) **Shirota et al. (2004) *J. Immunol.* 173:5002; "Shirota"**

Shirota states that suppressive oligodeoxynucleotides (ODN) can suppress Th1-mediated immune responses. Shirota, page 173, column 1, paragraph 2. Shirota states that a suppressive ODN was proven effective in the prevention/treatment of certain Th1-dependent autoimmune diseases. Shirota, Abstract. Shirota states that the study was undertaken to elucidate the mechanism whereby suppressive ODN would be effective in treating autoimmune disease. Shirota states that the findings "indicate that suppressive ODN selectively reduce Th1 cytokine production, while enhancing Th2 immunity." Shirota, page 173, column 2, first paragraph.

e) **Dong et al. (2004) *Arthritis Rheum.* 50:1686; "Dong 2004"**

Dong 2004 reports on the use of suppressive oligonucleotides (ODNs) to treat collagen-induced arthritis (CIA), a murine model of rheumatoid arthritis (RA), an autoimmune disease. Dong 2004 states that suppressive ODNs can inhibit the immune activation and arthritis induced by CpG motifs. Dong 2004, page 1686, column 2, first paragraph. Dong 2004 states that suppressive ODNs administered during the inductive phase of CIA significantly reduced the incidence and severity of arthritis. Dong 2004 states that treatment with suppressive ODNS significantly decreases serum titers of pathogenic IgG anti-CII autoantibodies and IFN-γ production by collagen-reactive T cells. Dong 2004 concludes that suppressive ODNs may be of therapeutic value in the treatment of RA, and potentially other autoimmune diseases." Dong 2004, page 1686, column 1, fourth paragraph. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

f) **Dong et al. (2005) *Arthritis Rheum.* 52:651; "Dong 2005"**

Dong 2005 describes the use of suppressive oligodeoxynucleotides (ODNs) for the treatment of autoimmune disease in an animal model of systemic lupus erythematosus (SLE). Dong 2005 states that

suppressive ODN significantly prolonged lifespan and delayed onset and progression of glomerulonephritis in the SLE mouse model. Dong 2005 concludes that suppressive ODN may be of benefit in the treatment of chronic systemic autoimmune diseases such as SLE. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

g) **Zeuner et al. (2002)** ***Arthritis and Rheum.*** **46:2219; "Zeuner"**

Zeuner describes the effect of suppressive oligodeoxynucleotides (ODNs) on CpG (ISS)-induced arthritis in an animal model. Zeuner states that administration of suppressive ODN reduced the manifestations and severity of arthritis up to 80%. Zeuner, page 2219, column 1, paragraph 4. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

h) **Gaupp et al. (2008)** ***Am. J. Pathol.*** **173:119; "Gaupp"**

Gaupp presents data showing that, in an experimental autoimmune encephalitis (EAE) animal model of multiple sclerosis, amelioration of encephalitis correlated with an up-regulation of Th2-type cytokines.

i) **Cheng et al. (2008)** ***J. Mol. Cell Cardiol.*** **45:168; "Cheng"**

Cheng states that suppressive oligonucleotides selectively reduce Th1 cytokine production, and have been proven effective at blocking the development of organ-specific autoimmune diseases.

j) **Jin et al. (2008)** ***J. Immunol.*** **180:58; "Jin"**

Jin describes a peptide, P277, that, when tandemly repeated, enhances a Th2 immune response in an animal model of type 1 (autoimmune) diabetes.

k) **Ramshaw et al. (Aug., 1997)** ***Immunol. Cell Biol.*** **75:409; "Ramshaw"**

Ramshaw discusses use of DNA vaccines for treating autoimmune disorders. Ramshaw notes that Th1 cells appear to be involved in many organ-specific autoimmune diseases, and that suppression of disease is associated with the Th2 phenotype. Ramshaw states that the induction of a Th2 response might be expected to have an effect on the course of autoimmune disease. Ramshaw provides data showing that DNA immunization induced a Th2 response and protected animals against EAE, a model of multiple sclerosis.

The Office Action stated that "Applicants provide a plethora of references … that demonstrate efficacy" and stated that "[t]his is not persuasive because it does not speak to the state of the art at the time the invention was made (1997) and does not utilize any specie within the claimed genus."

However, the possibility that the art does not "utilize any specie within the claimed genus" is irrelevant. What the art shows is that inducing a Th2 response is in fact effective to treat an autoimmune disease. As noted above, Applicants showed that an IIS induces a Th2 response. As such, those skilled in the art would reasonably conclude that an IIS-autoantigen conjugate would induce a Th2 response and would thus be efficacious in treating an autoimmune disorder.

Furthermore, Ho 2003 and Ho 2005 both discuss use of a GpG oligonucleotide comprising the sequence 5'-AAGGTT-3', which falls squarely within the IIS formula as recited in claim 32. As such, Ho 2003 and Ho 2005 both demonstrate efficacy of an oligonucleotide that falls within the recited formula.

Still further, Dong 2004 discusses use of suppressive oligonucleotides (ODNs) to treat collagen-induced arthritis (CIA), a murine model of rheumatoid arthritis, an autoimmune disorder. The suppressive ODN designated A151 discussed in Dong 2004 includes the sequence 5'-AGGGTTAGGGTTAGGGTT-3', or three copies of AGGGTT. The sequence AAGGTT falls squarely within the IIS formula as recited in claim 32. In addition, Dong 2005 discusses use of the same oligonucleotide (A151) for the treatment of autoimmune disease in an animal model of systemic lupus erythematosus.

Still further, Zeuner discusses use of suppressive oligodeoxynucleotides CpG (ISS)-induced arthritis in an animal model. The suppressive ODN discussed in Zeuner includes the sequence AAGCTT, which falls squarely within the IIS formula as recited in claim 32.

As to the criticism that the references cited are after the June 6, 1997 priority date, Applicants note that it is permissible to provide post-filing publications as evidence that the disclosure was in fact enabling when filed.[2]

Furthermore, it was known as of the June 6, 1997 priority date that inducing a Th2-type immune response can be used to treat an autoimmune disorder. The following publications are illustrative of the state of the art.

1) Liblau et al. (May 1997) *Int. Immunol.* 9:799; "Liblau"

Liblau is entitled "Experimental autoimmune encephalomyelitis in IL-4-deficient mice." Liblau states that Th1 $CD4^+$ T cells are responsible for EAE lesions, whereas Th2 $CD4^+$ T cells can suppress the disease process. Liblau, Abstract. Liblau states that the role of autoreactive Th2 responses as therapeutic down-regulates of EAE "has been firmly established." Liblau, page 801, column 2, paragraph 2.

[2] *In re Brana* 34 USPQ2d 1436, 51 F.3d 1560, 1567 (Fed. Cir. 1995)

2) Williams et al. (May 1997) *Proc. Natl. Acad. Sci. USA* 94:5290; "Williams"

Williams is entitled "Prevention of autoimmune disease due to lymphocyte modulation by the B-subunit of *Escherichia coli* heat-labile enterotoxin." Williams discusses autoimmune disease in the context of a murine model of arthritis. Williams states that injection of mice with type II collagen and CFA leads to arthritis, while a separate injection of *Escherichia coli* heat-labile enterotoxin (EtxB) at the same time as collagen challenge prevented leukocyte infiltration, synovial hyperplasia, and degeneration of the articular cartilage, and reduced clinical symptoms of disease by 82%. Williams states that protection was associated with a shift in the Th1/Th2 balance, and states that such a shift provides a means for treating autoimmune disease.

3) Pearson et al. (Feb. 1997) *J. Exp. Med.* 185:583; "Pearson"

Pearson is entitled "Induction of apoptosis and T helper 2 (Th2) responses correlates with peptide affinity for the major histocompatibility complex in self-reactive T cell receptor transgenic mice." Pearson states that many organ-specific autoimmune diseases are thought to be initiated by Th1 responses, and that protection, or recovery, is thought to be initiated by Th2 responses. Pearson, page 583, column 1.

4) Myers et al. (Feb. 1997) *Immunol.* 90:161; "Myers"

Myers is entitled "Suppression of murine collagen-induced arthritis by nasal administration of collagen." Myers reports that nasal administration of type II collagen (CII) reduced the incidence and severity of autoimmune arthritis. Myers states that downregulation of arthritis that occurs with intranasal administration of CII is associated with a Th2-type lymphokine profile. Myers, Abstract.

5) Bai et al. (May 1997) *Clin. Immunol. Immunopathol.* 83:117; "Bai"

Bai is entitled "IL-10 suppresses experimental autoimmune neuritis and down-regulates T_H1-type immune responses." Bai reports the effect of IL-10, a Th2-type cytokine, on experimental autoimmune neuritis (EAN). Bai states that recombinant human IL-10 can suppress clinical EAN, and that this suppression is associated with down regulation of Th1 responses and macrophage function, and upregulated Th2 responses.

6) Elias et al. (May 1997) *Diabetes* 46:758; "Elias"

Elias is entitled "Hsp60 peptide therapy of NOD mouse diabetes induces a Th2 cytokine burst and down regulates autoimmunity to various β-cell antigens." Elias states that a peptide of the human 60-kDa heat-shock protein (hsp60), designated p277, was found to be useful as a therapeutic agent to arrest the autoimmune process responsible for diabetes in NOD mice. Elias reports that the effectiveness of the p277 is associated with activation of a Th2-type response, and reduced Th1-type autoimmunity to hsp60.

7) Seder and Prussin (May 1997) *Int. Arch. Allergy Immunol.* 113:163; "Seder"

Seder is entitled "Are differentiated human T helper cells reversible?" Seder states that the Th2 phenotype has a beneficial role in mitigating autoimmune disease. Seder, page 163, column 1.

8) Zheng et al. (May 1997) *J. Immunol.* 158:4507; "Zheng"

Zheng is entitled "A noncytolytic IL-10/Fc fusion protein prevents diabetes, blocks autoimmunity, and promotes suppressor phenomena in NOD mice." Zheng states that administration of a noncytolytic IL-10/Fc fusion protein completely prevented the occurrence of diabetes in the noobese diabetic (NOD) mouse model of type 1 (autoimmune) diabetes. Zheng states that IL-10/Fc treatment inhibited expression of Th1-type cytokines and promoted expression of Th2-type cytokines.

9) Tian et al. (Dec. 1996) *Nat. Med.* 2:1348; "Tian"

Tian is entitled "Modulating autoimmune responses to GAD inhibits disease progression and prolongs islet graph survival in diabetes-prone mice." Tian states that in the NOD mouse model of autoimmune diabetes, β-cell-reactive Th1-type immune responses develop, resulting in destruction of the β-cells. Tian states that administration of a β-cell autoantigen induced a Th2 response , inhibited disease progression, and prolonged syngeneic islet graft survival.

The above-described references show that, as of the June 6, 1997 priority date, those skilled in the art would find it reasonable that inducing a Th2-type immune response can treat an autoimmune disorder. Furthermore, those skilled in the art, as of the June 6, 1997 priority date, recognized that administration of an autoantigen could ameliorate an autoimmune disease. The instant application demonstrates that administration of an IIS induces a Th2-type immune response. The instant application discloses that an IIS can be conjugated to an autoantigen. Because those skilled in the art knew, as of the June 6, 1997 priority date, that induction of a Th2-type immune response can treat an autoimmune disorder and that administration of an autoantigen could ameliorate an autoimmune disease, those skilled in the art would find it reasonable that an IIS-autoantigen conjugate could treat an autoimmune disorder.

<u>The art cited in the May 28, 2008 Office Action does not lead to a conclusion of lack of enablement.</u>

The May 28, 2008 Office Action cited various references; and stated that the art teaches that a Th1-Th2 cytokine switch or presence is not correlative of a therapeutic response. Applicants respectfully traverse.

As discussed previously, the art cited in the May 28, 2008 Office Action does not lead to a conclusion that instant claims 32-35, 38, 39, and 44 lack enablement.

The May 28, 2008 Office Action cited Louzoun et al. ((2001) *J. Autoimmunity* 17:311-321; "Louzon"); Brunet et al. ((2002) *Trends Immunol.* 23:127-128; "Brunet"); Genain et al. ((1996) *Science* 274:2054; "Genain"); and Hofstetter et al. ((2002) *J. Immunol.* 169:117-125; "Hofstetter").

Louzon

The Office Action stated that many investigators consider the Th1/Th2 paradigm an overly simplistic way to view highly complex systems; and cited Louzon.

Louzon presents a model that is stated to explain both the general agreement and the apparently contradictory results described by various groups. Louzon actually supports the Th1/Th2 paradigm. As such, Louzon does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Brunet

The Office Action stated that therapeutic manipulation of the Th1-Th2 balance is inherently dangerous and unpredictable; and cited Brunet.

However, Brunet does not discuss use of an IIS-autoantigen or IIS-autoantibody conjugate. As such, Brunet is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Furthermore, safety is not within the purview of the U.S. Patent Office; instead, safety considerations are within the purview of the U.S. Food and Drug Administration.

Genain

The Office Action stated that Genain teaches that immune deviation and shift of a cytokine production from a Th1 pattern to a Th2 pattern increased titers of autoantibodies, increase pathogenic autoantibodies and exacerbate autoimmune disease.

However, Genain discusses administration of myelin oligodendrocyte glycoprotein (MOG), which is said to be a minor constituent of myelin, to an experimental animal model of multiple sclerosis. Genain does not discuss use of an IIS-autoantigen conjugate. As such, Genain is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Hofstetter

The Office Action stated that the art teaches that autoimmune Th1 responses can develop and continue even in the presence and high frequencies of Th2 cells; and cited Hofstetter.

Hofstetter discusses administration of pertussis toxin (PT) to an experimental autoimmune encephalomyelitis (EAE) mouse, an experimental animal model of multiple sclerosis (MS). Hofstetter states that administration of PT to the EAE mouse prevented the protection from EAE conferred by injection of a peptide

that induced a Th2 response. The purpose of the study was to assess the various effects of PT on the pathogenicity, cytokine differentiation, and clonal sizes of neuroantigen-reactive T cells in EAE in mice. Hofstetter does not conclude that inducing a Th2 response is not helpful in treating an autoimmune disorder. Hofstetter merely analyzed the effect of PT on the protection conferred by injection of neuroantigens. As such, Hofstetter does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Hofstetter does not discuss use of an IIS-autoantigen conjugate. As such, Hofstetter is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Post-priority date references support the fact that claims 32-35, 38, 39, and 44 are enabled.

Others in the field recognize the usefulness of IIS in shifting an immune response from a Th1-type response to a Th2-type response; and recognize the usefulness of such a shift in, e.g., the treatment of autoimmune disorders.

As previously described, Ho 2003 and Ho 2005 provide further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

In addition, Dong 2004, Dong 2005, Shirota, and Zeuner, described in detail above, provide further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

The May 28, 2008 Office Action stated that "developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing." May 28, 2008 Office Action, page 7. However, it is well established that post-filing references can provide evidence of enablement, e.g., where the post-filing references describe successful carrying out of a method described in a patent application, or successful use of a composition described in a patent application.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 32-36, 38, and 39 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSD-173CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 14, 2009

By: /Paula A. Borden, Reg. No. 42,344/
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\UCSD\173con\UCSD173CON_Resp_FOA_021909.doc